Molecular motors: design, mechanism and control

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Biological functions in each animal cell depend on coordinated operations of a wide variety of molecular motors. Some of the these motors transport cargo to their respective destinations whereas some others are mobile workshops which synthesize macromolecules while moving on their tracks. Some other motors are designed to function as packers and movers. All these motors require input energy for performing their mechanical works and operate under conditions far from thermodynamic equilibrium. The typical size of these motors and the forces they generate are of the order of nano-meters and pico-Newtons, respectively. They are subjected to random bombardments by the molecules of the surrounding aqueous medium and, therefore, follow noisy trajectories. Because of their small inertia, their movements in the viscous intracellular space exhibits features that are characteristics of hydrodynamics at low Reynold's number. In this article we discuss how theoretical modeling and computer simulations of these machines by physicists are providing insight into their mechanisms which engineers can exploit to design and control artificial nano-motors.

I. INTRODUCTION

A cell, the structural and functional unit of life, in an animal body is not a passive bag of viscous multi-component fluid. The interior of a cell has lot of similarities with any modern city; just as there are streets, highways and railroad tracks on which traffic of vehicles move passengers and cargo in various destinations, intracellular molecular cargoes are also transported by wide varieties of molecular motors [1]. Not all molecular motors are, however, long-haul trucks. For example, muscle contraction associated with heartbeats are driven by a specific type of molecular motors which are specially designed for this purpose. So, it is not surprising that malfunctioning of the molecular transport system can cause diseases- traffic disruption or traffic jam can bring an entire traffic system to a standstill.

For obvious reasons, research on molecular motors has been a traditional area of research in molecular cell biology and biochemistry [2]. However, in recent years, this area of research has attracted physicists [3] as well as engineers [4]. How do these motors work? Exploring the design and mechanisms of these motors from an *engineering perspective* [4, 5] requires a investigation into their structure and dynamics using the fundamental principles of *physics* at the subcellular level. The insights gained from such fundamental research may find practical applications in designing and manufacturing artificial nano-motors. In contrast to man-made motors, the designs of natural nano-motors [6, 7, 8] have evolved over billion of years. In this article, while discussing the design, mechanism and control of molecular motors, we'll make comparisons with their macroscopic counterparts to emphasize their common features as well as their differences. We do not report new data in this article. But, we carry out an in-depth qualitative investigation of the similarities and diferences between the intra-cellular and man-made macroscopic motors keeping in mind the mixed readership of this journal.

A. Major components of the intracellular transport system

Just like the skeletons of human bodies, the cytoskeleton of an eukaryotic cell maintains its architecture. However, the cytoskeleton is not a rigid scaffold; it is a complex dynamic network that can change in response to external or internal signals. The cytoskeleton also serves as the network of tracks for the motors involved in intra-cellular transport processes. Moreover, the cytoskeleton plays important role in the motility of the cell as a whole.

The protein constituents of the cytoskeleton of eukaryotic cells can be broadly divided into the following three categories: (i) *Filamentous* proteins, (ii) *accessory* proteins, and (iii) *motor* proteins. The following three classes of filamentous proteins form the main scaffolding of the cytoskeleton (see fig.1): (a) *actin*, (b) *microtubule*, and (c) *intermediate filaments*. The three superfamilies of cytoskeletal motor proteins [9] are (see fig.4) (i) *myosin* superfamily,

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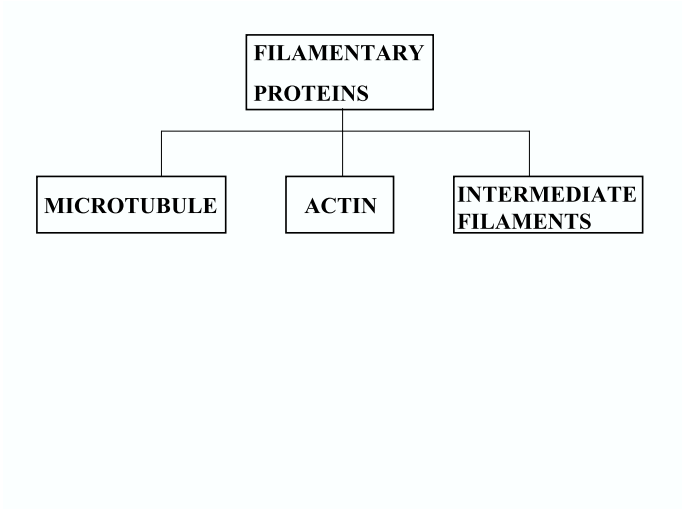

FIG. 1: The three classes of cytoskeletal filaments.

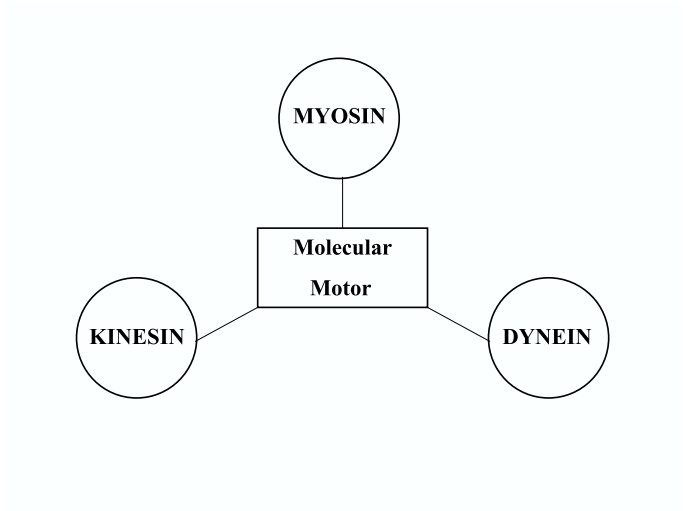

FIG. 2: The three superfamilies of cytoskeletal molecular motors.

(ii) *kinesin* superfamily, and (iii) *dynein* superfamily. Myosins either move on actin tracks or pull the actin filaments. In contrast, both kinesins and dyneins move on microtubules.

Nucleic acids (DNA and RNA) also serve as tracks for another class of motors which are, more appropriately, also referred to as nucleic acid translocases [10]. Just like cytoskeletal motors, these motors run on chemical fuel. But, instead of carrying cargo, these perform various other kinds of operations. For example, DNA helicase motors [11] unzip the two strands of double-stranded DNA and use one of the two strands as the track for its directed movement. RNA polymerases [12, 13] and ribosomes [14] are mobile workshops which polymerize RNA and proteins, respectively, while moving on the corresponding specific tracks which also serve as the template for the synthesis.

B. Processivity and Duty Ratio

One of the key features of the dynamics of cytoskeletal motors is their ability to attach to and detach from the corresponding track. A motor is said to be attached to a track if at least one of its heads remains bound to one of the equispaced motor-binding sites on the corresponding track. Moreover, a motor can detach completely from its track.

One can define processivity in three different ways:

(i) Average number of *chemical cycles* before detachment from the filament;

(ii) *attachment lifetime* of the motor to the filament;
(iii) *mean length* spanned by the motor on the filament in a single run.
The first definition is intrinsic to the process arising from the *mechano-chemical* coupling. But, it is extremely difficult to measure experimentally. The other two quantities, on the other hand, are accesible to experimental measurements.

During one cycle, suppose a motor spends an average time $\tau_o n$ attached to the filament, and the remaining time τ_{off} detached from the filament. Clearly, the period during which it exerts its *working* stroke is τ_{on} and its *recovery* stroke takes time τ_{off}. The *duty ratio*, r, is defined as the fraction of the time that each head spends in its attached phase, i.e.,

$$r = \tau_{on}/(\tau_{on} + \tau_{off}) \tag{1}$$

The typical duty ratios of kinesins and cytoplasmic dynein are at least 1/2 whereas that of conventional myosin can be as small as 0.01.

C. Design of filamentary tracks

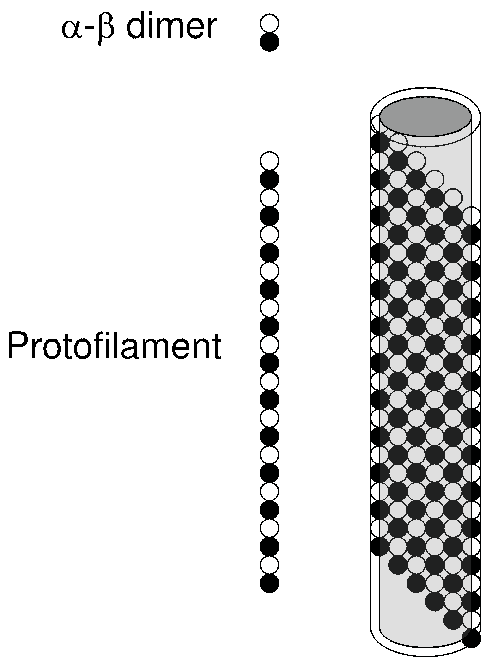

FIG. 3: A schematic presentation of a microtubule.

Microtubules are cylindrical hollow tubes whose diameter is approximately 20 nm (see fig.3). The basic constituent of microtubules are globular proteins called tubulin. Hetero-dimers, formed by α and β tubulins, assemble sequentially to form a protofilament. A sheet formed by the lateral organization of 13 such protofilaments then folds to form a microtubule. The length of each $\alpha - \beta$ dimer is 8 nm. Although the protofilaments are parallel to each other, there is a small offset of about 0.92 nm between the dimers of the neighbouring protofilaments. Thus, total offset accumulated over a single looping of the 13 protofilaments is $13 \times 0.92 \simeq 12nm$ which is equal to the length of three $\alpha - \beta$ dimers joined sequentially. Therefore, the cylindrical shell of a microtubule can be viewed as *three* helices of monomers (see fig.3). Moreover, the asymmetry of the hetero-dimeric building block and their parallel head-to-tail organization in all the protofilaments gives rise to the polar nature of the microtubules. The polarity of a microtubule is such an α tubulin is located at its - end and a β tubulin is located at its + end. Majority of the kinesins are + end directed motors whereas most of the dyneins are - end directed motor proteins. Since there is only one binding site for a motor on each dimeric subunit of MT, the minimum step size for kinesins and dyneins is 8 nm.

Filamentous actin are polymers of globular actin monomers. Each actin filament can be viewed as a double-stranded, right handed helix where each strand is a single protofilament consisting of globular actin. The two constituent strands

are half staggered with respect to each other such that the repeat period is 72 nm. Majority of myosins are + end directed i.e., move towards the "barbed" end of actin filaments [9].

II. DESIGN OF MOTOR PROTEINS

A central location in these molecular motors is occupied by the ATPase site which binds to ATP. The motor protein acts like an enzyme and catalyzes the hydrolysis of the ATP, releasing the products ADP and phosphate. This enzymatic change causes small changes in the conformation of the protein surrounding the ATPase site which, in turn, propagates to farther regions and, ultimately, gets amplified into interdomain movements. It is these conformational changes that generate sufficiently large forces responsible for the unidirectional motion of the motor over long distances through repeated enzymatic cycles.

There are several architectural similarities between the three superfamilies of cytoskeleton-based motor proteins, namely, kinesin, dynein and myosin. All the motor proteins have at least two different functional domains:
(i) *head*: this domain contains a site for ATP hydrolysis and a binding site for attachment to a cytoskeletal filament; and
(ii) *stalk*. In addition, all kinesin and dyneins have a *tail* domain which binds with the cargo.

However, in spite of these general qualitative similarities, there are quantitative differences in their structural features and also striking differences in their biological functions. For example, the head domain of the kinesins is the smallest, that of myosins is of intermediate size whereas the head of dyneins is very large. The tail domain exhibits much more diversity than the head domain because of the necessity that the same motor should be able to recognize (and pick up) wide varieties of cargoes. Majority of the members of myosin and kinesin superfamilies are homodimers although hetero-dimeric kinesins have also been discovered. Some members of myosin and kinesin superfamilies are known to self-assemble into higher-order structures. The most well known among these higher-order structures is the myosin thick filaments in muscles.

According to the widely accepted nomenclature, myosins are classified into families bearing numerical (roman) suffixes (I, II, ..., etc.). Unlike conventional myosin-II of skeletal muscles, which has a very low duty ratio (≤ 0.05), "unconventional" myosin-V and myosins-VI have quite high ($0.7-0.8$) duty ratios. Myosin-X has moderate duty ratio. Therefore, myosin-II are like "rowers" whereas myosin-V and myosin-VI are like "porters". Moreover, myosin-IX and myosin-VI are - end directed motors whereas all the other families of myosin are + end directed [16].

Kinesins are microtubule-based motor proteins. According to the latest standardized nomenclature of kinesins, the name of each family begins with the word "kinesin" followed by an arabic number (1, 2, etc.). Kinesin-1, the double-headed "conventional" kinesin, are "porters". Dyneins are microtubule-based motor proteins. The molecular architecture of the dyneins is the most complex among the cytoskeletal motors. These motors consist of at least ten subunits in addition to the large motor domain.

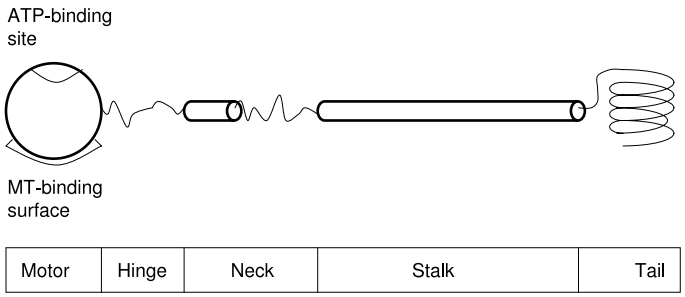

FIG. 4: A schematic representation of the organization of different domains in a typical kinesin motor (adapted from ref.[15]).

III. FUNDAMENTAL QUESTIONS

In this section, we list some of the fundamental questions on the mechanism of operation of the motors as well as their regulation and control. We phrase the questions in such a way that these may appear to be directly relevant only for the cytoskeletal motors. But, these can be easily rephrased for the other types of motors including, for example, those which move on nucleic acid strands. These questions are as follows [17]:
(i) **Fuel**: In case of macroscopic motors, we normally begin with the question whether the engine of the motor runs

on petrol, diesel, or electricity (or any other form of energy). The analogous question for molecular motors is: what is the *fuel* that supplies the (free-)energy input for the motor? The free energy released by the hydrolysis of ATP is usually the input for cytoskeletal motors.
(ii) *Engine, cycle and transmission*: The ATP-binding site on the motor, where ATP is hydrolyzed, can be identified as the engine of the motor. What are the distinct states of the cyclic engine in various stages of each cycle? Which step of the cycle is responsible for the generation of force (or, torque)? How is the structural (conformational) change, caused by this force (or torque), amplified by the architecture of the motor? In other words, how does the *trasmission* system of the motor work, i.e., what are the analogues of the *clutch and gear* of automobiles?
(iii) *Track and traction*: What is the nature of the filamentous track? Are they static or dynamic, i.e., do the lengths and/or orientations of the tracks change with time? What is the traction mechanism used by a motor head for staying on track, i.e., where is the track-binding site located in the motor head and how does it bind with the track? How is the traction controlled, i.e., how is the affinity of the motor head for its track altered by its binding with a fuel molecule, namely, ATP?
(iv) *Number of engines and coordination of their cycles*: Recall that an internal combustion engine may have more than one cylinder where fuel is burnt and phased movements of the pistons of these cylinders gives rise to a practically smooth continuous motion of the common shaft to which they are connected. How many heads does each cytoskeletal motor possess? Are all the heads identical? If not, what functional advantages arise from such heterogeity? Are the cycles of the different engines of a motor coordinated in any manner and, if so, how is this coordination maintained?
(v) *Stroke and step*: Recall that, while crossing a shallow stream by hopping on stones, the step size of a person is determined not necessarily by the length of his/her legs but primarily by the separation between the stones. A similar situation arises in the processive movements of motor on their tracks and, therefore, one has to distinguish between size of a *stroke* and that of a *step* [18]. The separation between the two successive binding sites on the track is the smallest possible step size of the motor. On the other hand, a stroke is a conformational change of the motor bound to the track and it takes the motor closer to its next prospective binding site on the track. In general, the stroke size need not be equal to the step size. If the motor covers only a fraction of the distance to the next binding site by the stroke, how does it manage to cover the remaining distance? Can the same motor adopt different step sizes under different circumstances? What features of the track or/and the motor determines the step size?
(vi) *Directionality and processivity*: What determines the direction of movement, i.e., why are some motors +-end directed whereas the others are −-end directed? Can a motor reverse its direction of motion (a) spontaneously, or (b) under an opposing (load) force? Do the motors possess reverse gears and is it possible to reverse the direction of their movement by utilizing the reverse gear mechanism? What is the minimal change (e.g., mutation) required to reverse the direction of motion of a motor? What is the mechanism that decides the *processivity* (or the lack of processivity) of a motor? The directionality and processivity of cytoskeletal motors involve coordination of essentially three cycles [19]: (a) ATP hydrolysis cycle, (b) the motor head-track binding cycle (periodic attachments and detachments of each motor head from the track), and (c) conformational cycle of the motor.
(vii) *Stepping pattern*: Does the motor move like an "inchworm" or does the stepping appear more like a "hand-over-hand" mechanism? Moreover, two types of hand-over-hand mechanism are possible: symmetric and asymmetric. In the symmetric pattern, the two heads exchange positions, but the three-dimensional structure of the molecule is preserved at all equivalent positions in the cycle. In contrast, in the asymmetric pattern, the two heads exchange position, but alternate steps differ in some way, e.g., what happens in "limping" which involves alternate faster and slower stepping phases. Can a motor switch from one track to a neighbouring track and, if so, how does it achieve that? What prevents a motor from changing lane on a multi-lane track?
(viii) *Speed and efficiency*: Is the average speed of a processive motor determined by the track or the motor or fuel or some external control mechanism? Recall that the average speed of a car on a highway in sparse traffic can be decided either by the smoothness of the highway, or by the model of the car (whether it is a Ferrari or a heavy truck), or by the quality of the fuel. Similarly, how does the molecular constitution of the track and the nature of the motor-track interaction affect the speed of the motor? Can an external force applied to a motor in the forward direction speed it up? Is the mechano-chemical coupling *tight* or *loose*? If hydrolysis of ATP provides the input free energy, then, how many steps does the motor take for every molecule of ATP hydrolyzed, or, equivalently, how many ATP molecules are consumed per step of the motor ? How does the speed of the motor depend on the opposing "load" force? What is the maximum speed it can attain? What is the stalling load force? What is the most appropriate definition of efficiency of the motor and how to estimate that efficiency?
(ix) *Regulation and control*: How is the operation of the motor *regulated*? For example, how is the motor switched on and off? Recall that the speed of a car can also be regulated by imposing the some speed limit or by traffic signals. Are there molecular *signals* that control the motor's movement on its track and how? How do motors get back to their starting points of the processive run after delivering their cargo?
(x) *Cargo*: What kinds of cargoes can be hauled by the motor? How does the motor pick up its cargo and how does it drop it at the target location?

Internal combustion engine	Coventional 2-headed kinesin
4 cylinders	2 heads
Combustion chamber	ATP-binding site
Firing the fuel	ATP hydrolysis
4 strokes of the Otto cycle in each cylinder	4 chemical states of the mechano-chemical cycle of each head
Common crank shaft connected to 4 cylinders	Stalk connected to 2 heads
Typical efficiency $\simeq 20\%$	Typical efficiency $\simeq 50\%$

TABLE I: Comparison of 4-cylinder internal combustion engine of macroscopic engines and 2-headed conventional kinesin nano-motor.

(xi) *Motor-motor interactions*: How do different types of motors interact while moving on the same track carrying their cargo? How do different classes of motors, which move on different types of tracks, coordinate their functions and even transfer or exchange their cargoes?

IV. MACRO- AND NANO-MOTORS: A COMPARISON

Several superficial qualitative analogies between the components of engines of macroscopic motorized vehicles (e.g., internal combustion engine) and those of cytoskeletal nano-motors are listed in table I. Moreover, qualitative similarities and quantitative differences between the processes underlying their operational mechanisms are also listed for the purpose of comparison.

Biomolecular motors operate in a domain where the appropriate units of length, time, force and energy are *nanometer*, *milli-second*, *pico-Newton* and k_BT, respectively (k_B being the Boltzmann constant and T is the absolute temperature). From table I, naively, one may think that the differences in the mechanisms of the molecular and macroscopic machines is merely a matter of two different scales (of size, time, force, energy, etc.). But, that is not true.

Since the masses of the molecular motors are extremely small, they are subjected to two dominating forces which are quite small for all the man-made macroscopic motors. Since the inertial forces are small compared to the viscous force, the dynamics of molecular motors is dominated by hydrodynamics at low Reynold's number. Moreover, the nano-motors are bombarded from all sides by the randomly moving water molecules. Because of these bombardments, the molecular motors experience an additional random force which leads to "noisy" trajectories of the motors. Furthermore, the active processes [20], in which these motors are involved, cannot be described by equilibrium statistical mechanics. Finally, it is worth pointing out that, unlike man-made motors, these natural nano-motors are capable of transducing chemical energy directly into mechanical work.

V. MODELING AND SIMULATION AT DIFFERENT LEVELS

Modeling molecular motors is a problem of mechano-chemistry; one has to capture the interplay of mechanical movements and chemical reactions. Such models can be developed at different *levels* of molecular details [21]. Even at a given level, the dynamics of the system can be formulated using different types of formalisms or updating rules for computer simulations.

(i) *molecular* level: In principle, one can write down the Newton's equations for all the atomic constituents of the motor and those of the surrounding aqueous medium. But, in practice, no molecular dynamics simulation of molecular motors is possible in forseeable future using these equations, because the duration of a single processive run of a cytoskeletal motor on its track is several orders of magnitude longer than the longest molecular dynamics simulation possible at present.

(ii) *Brownian* level: At this level one can treat the motor as a Brownian particle that moves in an energy landscape determined by the chemical reaction. For simplicity, we assume the motion to be restricted in one-dimensional space. The effects of the chemical reactions (e.g., ATP hydrolysis, etc.) are incorporated by asigning "internal" or "chemical states" to the motor. Therefore, in the overdamped regime, the dynamics of the center of mass of the motor x obeys the Langevin equation

$$0 = -\gamma \frac{dx}{dt} - \frac{dV_\mu(x)}{dx} + F_{ext} + \xi(t) \tag{2}$$

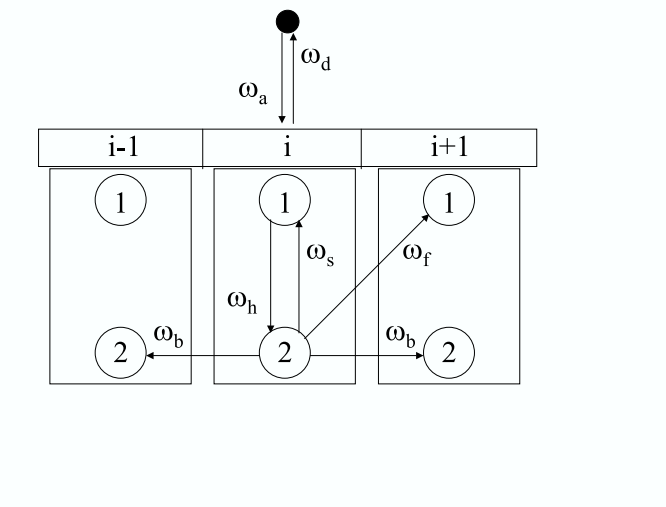

FIG. 5: A schematic description of the model reported in ref.[24] for a single-headed kinesin motor KIF1A. The symbols $..., i-1, i, i+1, ...$ label the motor-binding sites on the microtubule track. The allowed transitions are indicated by the arrows together with the corresponding rate constants, i.e., transition probabilities per unit time. Note that ω_a accounts for the possibility of attachment of motors to the microtubule track whereas ω_d accounts for the reverse process, i.e., detachment of bound motors (from ref.[25]).

where $V_\mu(x)$ is the potential experienced by the motor at the position $x(t)$ when it is in the "chemical" state μ. Moreover, as usual, F_{ext} is the externally applied mechanical force (the sign of the term will be negative in case of a load force) and $\xi(t)$ is the random Brownian force. The potential $V_\mu(x)$ evolves with time because of the chemical transitions. The chemical state evolves following the discrete master equation

$$\frac{\partial P_\mu(x,t)}{\partial t} = \sum_{\mu'} P_{\mu'}(x,t) W_{\mu' \to \mu}(x) - \sum_{\mu'} P_\mu(x,t) W_{\mu \to \mu'}(x) \tag{3}$$

In order to formulate the equivalent Fokker-Planck equations (more appropriately, a hybrid of Fokker-Planck and master equations), we define the probability $P_\mu(x,t)$ that at time t the center of mass of the motor is located at x while it is in the discrete (internal) "chemical state" μ. The equation of motion governing the time evolution of $P_\mu(x,t)$ is a combination of a Fokker-Planck equation and a master equation; the Fokker-Planck part describes the dynamics in continuous space while the Master equation accounts for the dynamics of transitions between discrete chemical states.

$$\begin{aligned} \frac{\partial P_\mu(x,t)}{\partial t} &= \frac{1}{\eta}\frac{\partial}{\partial x}\left[\{V'_\mu(x) - F\}P_\mu(x,t)\right] + \left(\frac{k_B T}{\eta}\right)\frac{\partial^2 P_\mu(x,t)}{\partial x^2} \\ &+ \sum_{\mu'} P_{\mu'}(x,t) W_{\mu' \to \mu}(x) - \sum_{\mu'} P_\mu(x,t) W_{\mu \to \mu'}(x) \end{aligned} \tag{4}$$

The Brownian level modeling has served well in elucidating the generic principles involved in the mechanisms of their directed transport [22, 23]. But, one of the difficulties of using this formalism for any specific member of a particular superfamily of motor proteins is that the potential $V_\mu(x)$ experienced by the motor is not available (unless derived from a more microscopic model for the combined motor-track system).

(iii) *Fully discretized chemical kinetic* level:

The kinetic rate equation formalisms are at a level higher than the Brownian level. In this approach one assumes a set of *discrete* states (i.e., discrete positions and discrete velocities) of the motor and the transitions between these states are given by appropriately chosen rate constants [3]. Some of the rate constants can depend on force and the form of the force-dependence is postulated on some physical grounds. This approach is based on the assumption that the phase space of the entire system, which is analogoues to a landscape, can be conceptually divided into a finite number of distinct regions each of which is like a deep valley in the landscape. A purely rate equation approach with discrete states is a reasonable approximation provided the barriers separating the valleys are sufficiently high. In principle, the rate constants can be derived from a more microscopic description like, for example, theories at the

ATP (mM)	ω_h (s^{-1})	v (nm/ms)	D/v (nm)	τ (s)
∞	250	0.201	184.8	7.22
0.9	200	0.176	179.1	6.94
0.3375	150	0.153	188.2	6.98
0.15	100	0.124	178.7	6.62

TABLE II: Transport properties of single-headed kinesin, at four different concentrations of ATP molecules, obtained from computer simulation of the model shown in fig.5 (from ref.[25]).

Brownian level. Alternatively, the phenomenological rate constants can be extracted from one set of empirical data and, then, can be used in all other situations for the same motor system.

VI. KINESIN MOTOR ON MT TRACK

It is now well established that the processivity of the double-headed conventional kinesin motor is, at least partly, because of the well coordinated out-of-phase ATPase cycles of the two heads which enables one of the heads to remain bound to the MT track while the other steps forward. However, an altogether different mechanism, based on Brownian ratchet concept [22, 23], had to be invoked to explain the experimentally observed processivity of single-headed kinesin. The model is shown shematically in fig.5. In the two "chemical" states labelled by 1 and 2 the motor head is bound, respectively, strongly and weakly to the MT track. This is a multi-step stochastic chemical kinetic model where both positions and chemical states of a motor are discrete. The detailed justification of this two-state model and the physical interpretation of the allowed transitions are given in ref.[24].

Carrying out computer simulations of this model, we computed some of the transport properties of the single-headed kinesin molecule; the results are listed in table II. In this table v is the average speed, D is the diffusion constant and τ is the average run time of the motors. These predicted values are in good quantitative agreement with the corresponding results obtained from *in-vitro* single molecule experiments.

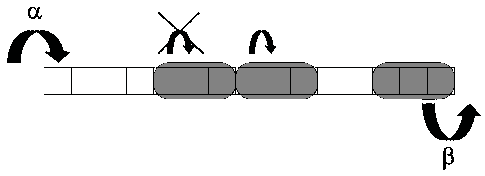

FIG. 6: A schematic description of the collective movement of interacting ribosomes on a single mRNA track.

VII. RIBOSOME TRAFFIC ON MRNA TRACK: FULLY DISCRETIZED CHEMICAL KINETIC MODEL

A protein is a bio-polymer, each characterized by a specific sequence of its monomeric subunits, called amino acids. Since these subunits are covalebtly linked by peptide bonds, proteins are also referred to as polypeptides. The polymerization of a polypeptide is carried out by a macromolecular complex, called ribosome [14], following the instructions encoded in the sequence of nucleotides in the template mRNA on which the ribosome moves as a motor. We assume that the initiation and termination of protein synthesis by each ribosome takes place with the rates α and β respectively; these rates are captured by imposing open boundary cnditions (OBC) on the system as shown in fig.6. Since a ribosome is much larger than a codon (a triplet of nucleotides) and we assume that each ribosome can simultaneously cover r lattice sites where each lattice site corresponds to a single codon. However, the position of a ribosome is denoted by that of the leftmost site it covers. Moreover, at each step a ribosome moves forward by one codon, i.e., a single lattice site. In order to capture the hard core steric interactions between the ribosomes, we impose the condition that no codon can be covered simultaneously by more than one ribosome.

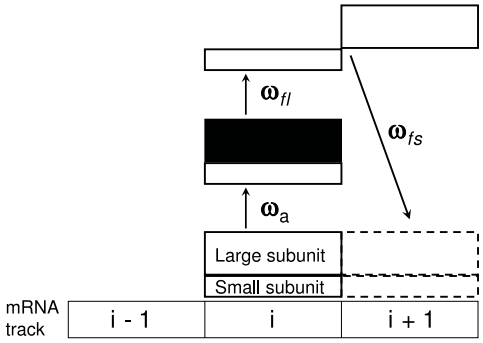

FIG. 7: A simple 3 state model of a ribosome during the elongation stage of protein synthesis.

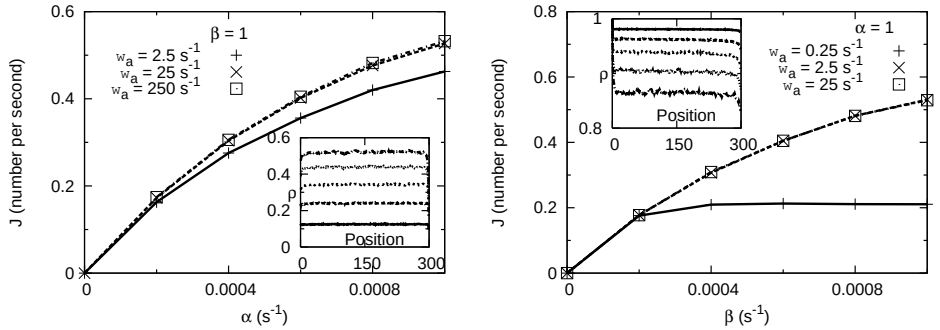

FIG. 8: Total rate of protein synthesis by ribosomes under open boundary conditions plotted against α in (a) and β in (b) for three values of ω_a. The discrete data points were obtained by doing computer simulations, and the curves are merely guides to the eye. The average density profiles are plotted in the insets. In the inset of (a) the lowermost density profile corresponds to $\alpha = 0.0002$, and the topmost one corresponds to $\alpha = 0.001$; α varies from one profile to the next in steps of 0.0002. In the inset of (b) the topmost density profile corresponds to $\beta = 0.0002$, and the lowermost one corresponds to $\beta = 0.001$; β varies from one profile to the next in steps of 0.0002. The other parameters are $\omega_{f\ell} = 1.8\ s^{-1}$ and $\omega_{fs} = 10\ s^{-1}$. (from ref.[27]).

For the purpose here, it is sufficient to note that (i) each ribosome consists of two subunits, called *large* and *small* subunits, respectively; (ii) the three major steps in the mechano-chemical cycle of a ribosome during the elongation of the polypeptide are as follows [27]:
(a) *arrival* of the correct amino-acid subunit in association with an adaptor molecule which, with the help of the ribosome, decodes the genetic message from the template track;
(b) following the formation of the peptide bond between the growing polypeptide and the newly selected amino acid, the larger subunit steps ahead by a codon on the mRNA track;
(c) stripped of its amino-acid subunit, which is now bonded to the growing polypeptide, the adapter molecule makes its final exit from the ribosome and the smaller subunit also steps forward to the next codon.
These three steps of the mechano-chemical cycle are shown schematically in fig.7 together with the corresponding rate constants. We'll not go into the finer details of the processes involved in polypeptide synthesis [26].

We define the flux J as the average number of ribosomes crossing the stop codon per unit time. The flux of the ribosomes gives the total rate of synthesis of the polypeptides. Although it is possible to compute this quantity for any given codon sequence on the mRNA template [26], we present here the data for the simple case of a homogeneous sequence [27].

The flux of the ribosomes, i.e., the total rate of protein synthesis, obtained from computer simulations of the model defined by the figs. 6 and 7 are plotted in fig.8(a) and fig.8(b) as functions of α and β, respectively. The average density profiles observed for several values of α and β are also shown in the insets of figs. 8(a) and (b). For $\alpha < \beta = 1$, the flux increases, and gradually saturates as α increases because higher α corresponds to a higher rate of initiation of protein synthesis. This increase of flux with increasing α is also consistent with the corresponding higher average density profile shown in the inset of fig. 8(a). For $\beta < \alpha = 1$, the increase, and gradual saturation, of flux with increasing β is caused by the weakening of the bottleneck at the stop codon. This trend of variation of flux with β is also consistent with the gradual lowering of the average density profile with increasing β (see the inset of fig. 8(b).

Motor	Track
Dynein	Microtubule
Kinesin	Microtubule
Myosinsin	Actin filament
DNA helicase	ssDNA
RNA helicase	RNA
DNA polymerase	ssDNA
RNA polymerase	ssDNA
Ribosome	mRNA

TABLE III: Some common intracellular molecular motors and the corresponding tracks.

Similar results have been reported recently [28] also for the traffic of RNA polymerase motors on DNA tracks during the synthesis of RNA.

VIII. SUMMARY AND CONCLUSION

In this article we have illustrated the use of models and computer simulations for studying the mechanisms of molecular motors by applying the technique to two particular cases. A list of some common intracellular molecular motors and their filamentary tracks is given in table III; however, this list is far from complete.

How are the motors regulated? The experimental data strongly indicate that, perhaps, there is no universal or generic mechanism for regulating the operation of molecular motors. It is widely believed that, because of the higher architectural complexity and association with several accessory proteins, dyneins may be regulated in several ways which are not possible in the simpler cases of kinesin and myosin motors [29]. The mechano-chemical pathways of motors are related to their function. The speed of operation of a motor can be controlled either by varying the concentration of the fuel or ligands or by applying external force which alters the rate of the chemical reactions [30].

It is amusing to note that molecular motors have no wheel. The cytoskeletal motors we have considered in this article are, at least structurally, more like "porters" walking along a track carrying load on their heads. In fact, there are some related non-processive cytoskeletal motors which work collectively in a manner that has strong similarity with "rowers" of boats. In addition to the "linear" motors, which move on filaments, cells also use rotary motors. In fact, to our knowledge, the smallest rotary motor is the ATP synthase [31] which is used by every animal cell to synthesize ATP, the most common fuel for intracellular machineries. Another rotary motor, somewhat larger than ATP synthase, is the bacterial flagellar motor [32] which rotates the flagellum that is responsible for bacterial locomotion in aqueous media. We hope to report exciting new developments in computer simulations of some of these motors in near future.

Efforts are being made to exploit the lessons learnt from the studies of natural nano-motors to design and manufacture artificial nano-motors [33]. Two different strategies are being following in such bottom-up approaches. In one of these integrates the components of the natural motors into an artificial scaffold so as to get the required performance of the machine. In the alternative approach, one synthesizes a fully artificial motor molecule whose design mimics the design of its natural counterpart. However, several practical hurdles remain on the path of commercialization of nano-machines. Neverthless, nano-robotics [4] may no longer be a distant dream.

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